Author's response to reviews

Title: Chronic low back pain is associated with reduced vertebral bone mineral measures in community-dwelling adults.

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Author's response to reviews: see over
6 January 2012

Dr Frank Roemer
BMC Musculoskeletal Disorders
Re: MS 1000158056637145 - Chronic low back pain is associated with reduced vertebral bone mineral measures in community-dwelling adults.

Thank you for your email on 5 January 2012 and for arranging peer review of this manuscript. I am pleased to be able to respond to the reviewers’ comments, as outlined point-by-point below. The manuscript has been revised using track changes. Thank you for considering this revised manuscript for publication in *BMC Musculoskeletal Disorders*.

Sincerely,

Dr Andrew Briggs
Chief author.
Response to reviewers

Editor’s comments

1. The discussion should be shortened and re-focused on to the main findings of the study (see also remark by reviewer 2).

   The discussion has been shortened to deal with only the main aspects of the study.

2. Cut reference list to 30-40 maximum. Please choose the most relevant ones in regard to study.

   The reference list has been reduced to 35 by removing references throughout the manuscript.

3. Please clearly acknowledge in discussion that one major limitation is the low number of subjects analysed (n=29).

   The limitation of the small sample size has been made more explicit in the discussion (first and last paragraphs).

4. Manuscript needs to be revised according to reviewers’ remarks.

   The manuscript has been revised according to the reviewers’ comments. See the point-by-point response below.

5. Acknowledgement: Please place the 'Acknowledgement' section after 'Author’s Contribution' section.

   The acknowledgement section has been moved.

Reviewer 1: Jun Iwamoto

1. What is the mechanism for the occurrence of CLBP related to lower BMD? Did CLBP reduce BMD or did lower BMD cause CLBP? How come lower BMD was associated with CLBP?

   While the reviewer raises a critical question, this issue cannot be addressed in the context of the current study. This is a cross sectional study, and therefore an inference around causation cannot be made. In order to determine causation, a prospective study would need to be undertaken. We did report an association between lower BMD and CLBP and the potential mechanisms underlying this observation have been discussed in the manuscript, as well as our earlier theoretic framework paper 1. Some additional commentary to explain the association has been added to the Discussion. However, the potential LBP-related predictor variables we included in this study (psychological wellbeing, back muscle endurance and physical activity) were not associated with DXA parameters, suggesting that other factors may drive the relationship between bone health and CLBP in this cohort. We can speculate on what these factors may be (as included in the Discussion), but cannot comment with certainty since no further data were collected.

2. Did the subjects with CLBP have some clinical risk factors for lower BMD?

   The potentially confounding effect of clinical risk factors for lower BMD was controlled in this study among for both participants with CLBP and controls. As described in the methods, known clinical risk factors for osteoporosis / low BMD were treated as exclusion criteria. These criteria were applied to the entire study...
cohort so that the current study only included those people without known risk factors for low BMD. As detailed in the Methods, the risk factors included:

- Aged greater than 60 years to minimise the potential effect of age-related bone loss and spinal degenerative conditions.
- Currently smoking on all or most days or a history of smoking on all or most days in the last 10 years considering the association between smoking and bone loss.
- A period of immobilisation of \( \geq 6 \) weeks within the last 12 months to minimise the deleterious effects of immobilisation on bone mass.
- Health conditions known to affect aBMD other than primary osteoporosis and osteopenia (rheumatoid arthritis, osteomalacia, Padget’s disease, Cushing’s syndrome, ankylosing spondylitis) to exclude the influence of co-morbidities on aBMD.
- Medications known to affect aBMD (oestrogen, progesterone, bisphosphonates and other osteoporosis therapies) which have been taken for \( \geq 6 \) months to exclude pharmacologically-mediated effects on bone.
- Menarche delayed beyond 16 years of age, cessation of normal menstrual periods prior to the age of 45 other than cases of hysterectomy and women more than 5 years post menopause to exclude the potential deleterious effect of reduced circulating oestrogen on aBMD.
- Body mass index (BMI) <18 or >30 to exclude the influence of low body weight and obesity on aBMD measures and accuracy of densitometer performance.

Further, the Discussion section acknowledges that other risk factors, for which data were not collected in this study, may also contribute to lower bone mass. The limitation of not collecting data on these factors has been acknowledged in the Discussion.

3. BMD and BMC are key data in this study so that information about the reproducibility of DXA measurements needs to be given somewhere.

The reproducibility of the DXA PA and lateral-protection measurements has been included in the Methods section of the paper, citing references. The reproducibility of DXA parameters for the densitometer used in the laboratory has been established previously for body composition measures while data from a pilot study for PA-projection aBMD in the lumbar spine indicated excellent short-term reproducibility (%CV: 1.1%), based on a test ret-test study of 8 participants.

4. T or Z scores of bone mineral measures must be discussed. Did some of the study subjects with CLBP have low BMD corresponding to osteoporosis or osteopenia?

The T-scores for the PA-projection total spine data have been added to Table 1 in the manuscript. The range of T scores for males and females have been added to the results section. The T-scores for L3 and lateral-projection data have not been included for two reasons: i) reliable T-scores for lateral-projection data are not available for males, and ii) T-scores for single vertebrae and those derived from lateral-projection scans should not be used for diagnostic purposes, according to the position statement of the International Society for Clinical Densitometry. Further, Z-scores are not used for diagnostic purposes according to the WHO criteria for the diagnosis of osteopenia and osteoporosis. It is reasonable that some T scores will be in the osteopenia or osteoporosis range (ie < -1.5), due to a number of factors, one of which may be CLBP. Indeed, the aim of this study is to determine whether an independent association exists between aBMD and CLBP.

5. Although physical activity was evaluated, occupation may also be important because it could influence the occurrence of LBP. Posture in terms of alignment of the spine (scoliosis, lordosis, and kyphosis) is also an important factor. Discuss these issues.

The reviewer highlights potentially important factors which may influence the association between the
presence of CLBP and aBMD. Occupational factors are likely to influence the magnitude and frequency of skeletal loading through physical activity (and inactivity) and may also exert an influence on hormonal factors, such as cortisol, which can influence bone density. Similarly, posture (either habitual or occupational) can influence skeletal loading which may have implications for aBMD in the lumbar spine. These factors should be considered in future research and are now noted in the Discussion.

6. Strength and limitation need to be discussed.

The strengths and limitations of the study have been discussed in the final paragraph of the Discussion section of the manuscript. Some elements of this section have been revised, taking into account the comments raised by the Editor and other reviewer so that the components are presented more explicitly, while at the same time attempting to reduce the length of the Discussion as requested by the Editor and other reviewer.

Reviewer 2: Frances Williams

1. The introduction ignores large literature on disc degeneration (including studies of 1000s using MRI) and its relationship with LBP and, more recently, BMD. At the very least comparison should be made with conventional DXA results in the same sample.

The reviewer is correct in that many studies have examined the association between low back pain and intervertebral disc degeneration, yet the association between clinical symptoms and disc degeneration for non-specific low back pain remains equivocal. Nonetheless, the association between disc degeneration and spinal BMD is relevant. This association was not the focus of the study and for this reason was not included explicitly in the literature review. However, paragraph 2 of the Introduction refers to the range of biopsychosocial factors which may influence bone health and references a comprehensive review paper on this issue\(^1\). The review paper discusses the associations between disc degeneration, BMD and low BMD. Nonetheless, to address the reviewer’s concern a commentary has been added to the Introduction concerning the relationship between intervertebral disc degeneration (common in LBP) and BMD (refer to paragraph 3) and also to the Discussion.

While disc degeneration may influence BMD (eg as reported by Livshits et al\(^3\)), the association is most likely influenced by the manner in which BMD is measured. For example, histologic data demonstrate that disc degeneration influences bone mass in different subregions of the vertebral body\(^4\) (some subregions increasing and some areas decreasing) which is likely attributable to the altered transmission of axial loads through the vertebral body in the presence of disc degeneration\(^5,6\). While gross BMD in the spine, for example measured with PA-projection DXA, may be positively associated with disc degeneration, this does not necessarily imply that disc degeneration is protective against vertebral fragility, supported by a large body of literature. A full discussion of these issues is beyond the scope of this paper, particularly in light of the Editor’s request to reduce the length of the Discussion and references.

2. The sample size is too small (29 cases) for a decent epidemiological study. It has been shown using MRI that degenerative change starts in young adults, thus a sample using an upper age limit of 60 will definitely include a substantial proportion of subjects with lumbar disc degeneration (LDD).

The reviewer is correct that the sample size is small, and this limitation has been written more explicitly in the Discussion (see Editor’s comment 3). The purpose of this study was not to undertake a large epidemiological investigation. Rather, this study represents a component in an iterative programme of research. We initially undertook a compressive literature review to develop an evidence-informed theoretic framework to explain a potential association between CLBP and bone health\(^1\). The current study was subsequently undertaken to address the limitations of earlier investigations (specially related to bone
densitometry methods and characterisation of CLBP) and provide a snapshot of evidence. Given the finding in this small study, it is now appropriate to undertake a larger epidemiological study to verify the findings, using the protocols and framework developed for this small study.

3. Extensive discussion and 80 references suggest there is little novel to discuss pertaining to scant data collected in this study.

The number of references and length of the Discussion have been reduced to address this comment and the Editor’s comment.

References